Tetrahedron Letters,Vol.27,No.37,pp 4505-4506,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

THE ISOLATION OF A SPIRAN IN THE REARRANGEMENT OF AN α-BROMO-α,β-UNSATURATED STEROIDAL KETONE

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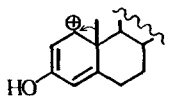
Abstract: A new acid-catalyzed aromatization of 3-bromocholest-2-en-4-one has been found and a spiranic product is really captured in this rearrangement.

The dienone-phenol rearrangement was studied during investigations of possible routes to the oestrogenic hormones, and numerous rationalizations of the exact mechanisms have been reported in an attempt to explain the anomalous results.[1] At present, only two reaction paths are generally acceptable: one involves 1,2-shift of angular methyl group in a carbonium ion(1) and another involves double 1,2-shifts of alkyl group(C-9) via a cationic spiran intermediate(2). To our knowledge, however, no spiran has ever been isolated in the acid-catalyzed aromatization of steroidal ring A.



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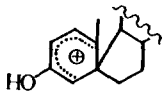

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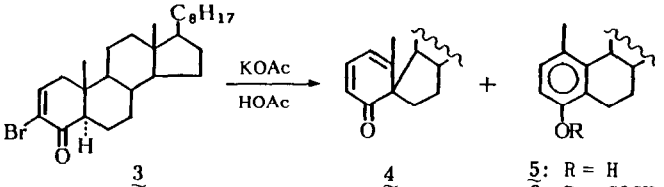
We now report the isolation of a spiran from the new dienone-phenol type rearrangement of an α-halo-α,β-unsaturated steroidal ketone. As the most suitable substrate we selected 3-bromocholest-2-en-4-one[2] (3), because α-bromo-α,β-unsaturated ketones are at the same level of oxidation as dienones they might aromatize by a dienone-phenol type pathway. In practice, successful aromatization and isolation of the target spiran were achieved by the treatment of the bromo-enone (3) under acetolytic conditions, whereas the substrate is stable under the other acidic conditions.[3]



3 4 5: R = H 6: R = $COCH_3$

A solution of 3 with a 33 fold excess of potassium acetate in glacial acetic acid was heated under reflux in a nitrogen atmosphere. The reaction was complete in 20 hr (t.l.c.). After usual treatment, Lobar column chromatography of the crude product gave the desired spiran (4; 21.6%) and aromatic steroids (5; 31.7%, 6; 5.6%).

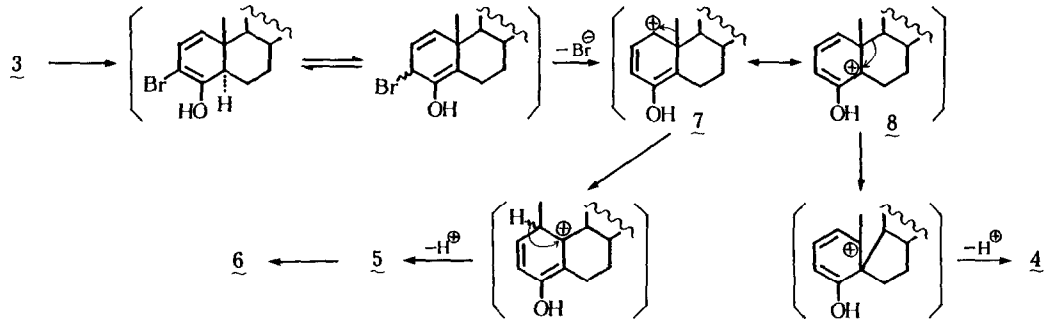
The spiran 4 and other phenolic products are unknowns and the structures were confirmed by spectroscopic analyses[4] as follows. In the IR spectrum 4 shows absorption bands at 1658cm^{-1} due to a carbonyl group and at 1625 and 1560cm^{-1} due to double bonds. The UV spectrum exhibits λmax 323nm (ε 7200). The ^{1}H-NMR spectrum shows a 3H singlet at δ 2.02 which can be attributed to the methyl group attached to an olefinic carbon atom(C-10) and three olefinic proton signals at δ 5.93(d), 6.07(d), and 6.95(dd). Particularly, the correctness of C-5-spiran structure has been supported vigorously by the fact that the ^{13}C-NMR spectrum shows a singlet at δ 65.39 attributed to C-5.

The IR spectrum of the phenol 5 shows bands of OH (3610cm^{-1}) and of aromatic ring (1590cm^{-1}). The UV spectrum exhibits λmax 285nm (ε 2000). The ^{1}H-NMR spectrum shows a characteristic broad

doublet (J=14.5Hz, W_H=7.0Hz) at δ 2.80 due to 6α-hydrogen under the deshielding effects of 4-hydroxyl group[5] and two doublets at δ 6.55 and 6.85 (J=8.8Hz) due to the aromatic hydrogens. The ^{13}C-NMR spectrum shows signals at δ 47.05(q, C-19), 111.58(d, C-3), 124.61(s, C-5), 128.91(s, C-1), 129.07 (d, C-2), 140.54 (s, C-10), and 151.33 (s, C-4). Acetylation of 5 with acetic anhydride-pyridine gave 6.

We also inquired into the possibility of further alkyl migration in the spiranic structure(4) to form a phenolic product: actually 4 was further treated with potassium acetate in glacial acetic acid and was also attempted to aromatize under the other acidic conditions,[3] but in all cases, the compound was found to be stable and was surely recovered unchanged.

Thus, the reaction can be envisaged as proceeding through two mechanistic paths via mesomeric dienol cations(7 and 8). The formation of the spiran probably proceeds via migration of C-9-10 bond



to C-5, with subsequent loss of the proton from the enol. Whereas the formation of the 1-methylphenol(5) might involve a simple 1,2-shift of the angular methyl group from C-10 to C-1.

These experiments represent the first example of the isolation of a spiran from the acid-catalyzed rearrangement of steroidal hormones, supporting the intermediacy of such systems in this type of reactions.

References

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2. C.W. Shoppee and R.E. Lack, J. Chem. Soc., 1961, 3271.

3. Actually treated with (1) sulfuric acid in acetic anhydride, (2) *p*-toluenesulfonic acid in acetic anhydride, and (3) zinc chloride in acetic acid and acetic anhydride, respectively.

4. Satisfactory IR, UV, NMR, and mass spectra, and elemental microanalyses were obtained for all new compounds. Selected data as follows:
4: colorless needles, m.p. 106-107 °C (from n-hexane), ^{1}H-NMR δ : 2.02 (3H, s, 10-Me), 5.93 (1H, d, J=9.5Hz,1-H), 6.09 (1H, d, J=6.4Hz, 3-H), 6.95 (1H, dd, J=6.4, 9.5Hz, 2-H). ^{13}C-NMR δ : 43.66 (s, C-13), 45.13 (q, C-19), 65.39(s, C-5), 119.89(d, C-1), 123.41(d, C-3), 141.83(d, C-2), 155.53(s, C-10), 208.73(s, C-4).
5: colorless needles, m.p. 143-144 °C(from MeOH), ^{1}H-NMR δ: 2.30(3H, s, 1-Me), 2.80(1H, br. d, J= 14.5Hz, W_H= 7.0Hz, 6α-H), 6.55(1H, d, J=8.8Hz, 3-H), 6.85(1H, d, J=8.8Hz, 2-H).
6: colorless needles, m.p. 69-70 °C (from MeOH), ^{1}H-NMR δ: 2.23 (3H, s, OAc), 2.32 (3H, s, 1-Me), 6.73 (1H, d, J= 8.2Hz, 3-H), 6.98(1H, d, J=8.2Hz, 2-H).

5. M. Tomoeda, M. Inuzuka, T. Furuta, and T. Takahashi, Tetrahedron Letters, 1964, 1233.

(Received in Japan 14 June 1986)